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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
WEHBE, ANNE MARIE SABRINA	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 09/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

SM

Office Action Summary	Application No.	Applicant(s)	
	09/903,327	NEMEROW ET AL.	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 7/28/04.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 2-15,18-27,30,32,34,36,37,40 and 42-51 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 2-15,18-27,30,32,34,36,37,40 and 42-51 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/28/04 has been entered. Applicant's amendment and response received with the RCE have also been entered. Claims 16, 33 and 41 have been canceled and new claims 46-51 have been added. Claims 2-15, 18-27, 30, 32, 34, 36-37, 40, and 42-51 are currently pending and under examination in the instant application. An action on the merits follows.

Those sections of Title 35, US code, not included in this action can be found in previous office actions.

Applicant's amendment fails to comply with the revised amendment practice as required by 37 CFR 1.121(c). See also 37 CFR 1.111. Claim 2 indicates that it was " previously amended". However, the claim contains a new amendment striking out the word "phosphatidylinositol". As such, the claim should be labeled as " currently amended". While applicant's response has been considered in the interests of compact prosecution, please note that further amendments must comply with 37 CFR 1.121(c).

Claim Rejections - 35 USC § 112

The rejection of claims 13-14, 33, 37, and 40, under 35 U.S.C. 112, second paragraph, for indefiniteness is withdrawn in view of applicant's amendment and or cancellation of the claims.

Applicant's amendments to the claims have resulted in the following new grounds of rejection.

Claims 2, 15, 18-19, 36, 40, 44, and 46-51 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 has been amended to remove the word "phosphatidylinositol". The claim now reads, "..wherein the targeting agent or portion thereof that triggers 3-OH kinase (PI3K) ..". The claim is confusing since neither the art nor the specification discloses a "3-OH kinase", and PI3K refers to phosphatidylinositol 3-OH kinase. Therefore, the metes and bounds of the claim are unclear. It is suggested that the applicant amend claim 2 to re-recite phosphatidylinositol in order to overcome this rejection.

Claim 15 lacks antecedent basis for "a targeted receptor". Claim 15 depends on claim 32 which recites that the bifunctional molecule binds "a targeted cell surface protein".

Claim 18 is indefinite in its recitation that the antibody or portion thereof binds to penton "fiber". Claim 18 depends on claim 32 which recites that the adenovirus is "fiberless".

Therefore, the limitation of claim 18 conflicts with independent claim 32. As such, the metes and bounds of the claim are unclear.

Claim 19 depends on claim 32 which recites that the antibody binds to penton. Claim 19 however recites a broader limitation, wherein the antibody binds to an antigen that includes an RGD motif. Since many proteins contain RGD motifs other than penton, the scope of claim 19 is unclear and appears to conflict with the scope of claim 32.

Claim 36 as amended is confusing. The claim as amended reads, "… whereby interaction with α_v integrin of an adenovirus particle displaying the bifunctional molecule is bypassed α_v integrin;…" . The claim as written is confusing because it is unclear what is meant by "bypassed α_v integrin". Deletion of the second recitation of bypassed α_v integrin would overcome this rejection. Since claim 44 depends on claim 36, it is also rejected as indefinite.

Claim 46 is confusing in the recitation, ".. an antibody or antigen-binding portion". Since the claim does not recite, " antigen-binding portion thereof", it is unclear whether the "portion" is meant to encompass proteins other than an antibody. Thus, the metes and bounds of the claim cannot be determined. Amending the claim to recite, "antigen-binding portion thereof" would overcome this rejection.

Claims 47-51 depend on claim 46 and thus are also indefinite. In addition, claims 47-51 lack antecedent basis for , "The targeted delivery vector particle of claim 46". Claim 46 recites an adenoviral particle, not a targeted delivery vector particle. It is also noted that claims 47 and 51 lack antecedent basis for , "antibody or portion thereof", since claim 46 does not recite, "a portion thereof".

Claims 2-9, 12, 15, 18, 20-27, 30, 32, 34, 36-37, 40, 44, and 46-51 are newly rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a targeted delivery vector particle, comprising: (a) a fiberless adenovirus particle; (b) a bifunctional molecule, comprising and antibody or antigen-binding portion thereof and a targeting agent, wherein; the antibody or antigen-binding portion thereof specifically binds to an RGD motif in penton on the particle, whereby the bifunctional molecule is linked to the particle and interaction of the particle with α_v integrin is bypassed; and the targeting agent specifically binds to a cell surface protein that activates the phosphatidylinositol 3 (PI3) signaling pathway; and (c) a fiberless adenovirus genome in the particle, does not reasonably provide enablement for said targeted delivery vector particle wherein the adenovirus particle is not fiberless or wherein the antibody does not bind to an RGD motif in penton. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The specification does not provide an enabling disclosure for bypassing α_v integrin interaction between a target cell expressing α_v integrin and a targeted adenoviral delivery vector particle comprising complexing an adenoviral particle comprising fiber with a targeting bifunctional molecule wherein the bifunctional molecule comprises an antibody that specifically binds to an RGD motif in penton. This grounds of rejection only applies to claims 46-51. New claims 46-51 broadly read on adenoviral particles which may or may not contain fiber. The prior art and the specification teach that the fiber protein expressed in the capsid of adenoviral particles naturally target cells which express the Coxsackie Adenovirus Receptor (CAR) . Following binding of CAR by the fiber knob, the adenoviral particle is internalized in clathrin

coated pits in a process which requires the interaction between the penton base and α_v integrin on the target cell surface (see the instant specification and Stewart et al. (1997) EMBO, Vol. 16 (6), 11289-1198, see page 1189). The specification further teaches that adenoviral particles can be modified to bypass CAR and integrin interactions by complexing the adenovirus with a bifunctional molecule that comprises an antibody that binds to penton and targeting agent that binds to a PI3 kinase on the target cell surface. The specification provides a working example wherein an adenoviral particle comprising fiber is complexed with a bifunctional molecule comprising the DAV-1 antibody which specifically binds to the RGD motif in penton and TNF, wherein the binding of TNF to TNF receptor on the target cell results in particle internalization. The working examples, however, clearly demonstrate that despite the presence of the bifunctional molecule on the target cell, internalization is mediated by both CAR-fiber internalization and TNF-receptor association (see the instant specification, pages 88, lines 23-31, and page 89, lines 1-12). The specification's own working examples therefore demonstrate that adenoviral particles comprising fiber complexed with a bifunctional molecule as claimed do not fully bypass α_v integrin interaction. While the applicants do not speculate on the reason why the particles continue to interact via fiber and penton, Stewart et al. explains that RGD epitopes in penton on adenovirus escape antibody neutralization due to steric hindrance from the adenovirus fiber (Stewart et al., *supra*, page 1189, abstract, and page 1196, column 1). Thus, in the presence of fiber, the binding of anti-RGD antibodies to the adenoviral particle does not bypass the interaction of the particle with α_v integrin since not all RGD sites are bound by the antibody due to steric hindrance. Therefore, based on the nature of adenovirus particles comprising fiber, the data provided in the working examples which demonstrates that that

adenoviral particles comprising fiber complexed with a bifunctional molecule as claimed do not fully bypass α_v integrin interaction, the evidence in the prior art that fiber sterically hinders antibody binding to the RGD motif in penton, the skilled artisan would not have predicted success in making or using an adenoviral particle comprising fiber and a bifunctional molecule as claimed, wherein the particle bypasses α_v integrin interaction on a target cell.

The specification further does not provide an enabling disclosure for bypassing α_v integrin interaction between a target cell expressing α_v integrin and a targeted fiberless adenoviral delivery vector particle comprising complexing a fiberless adenoviral particle with a targeting bifunctional molecule wherein the bifunctional molecule comprises an antibody that specifically binds to penton, wherein the antibody portion of the bifunctional molecule does not bind to the RGD motif in penton. This grounds of rejection only applies to claims 2-9, 12, 15, 18, 20-27, 30, 32, 34, 36-37, 40, 44, 46, 48, and 50-51. These claims read broadly on fiberless adenoviral particles comprising a bifunctional molecule comprising an antibody portion that specifically binds to penton, resulting particle bypasses α_v integrin interaction between penton and α_v integrin. As noted above, the prior art and the specification teach that penton binds to α_v integrin via an RGD motif present in the penton base (see Stewart et al., *supra*, page 1189, and the instant specification). While the specification and the prior art teaches that monoclonal antibodies which bind to the RGD motif in penton can inhibit adenoviral interaction with cell surface α_v integrin and internalization, neither the specification nor the prior art teaches that any other motif in penton associated with α_v integrin or that the binding of an antibody to any epitope in penton other than an epitope comprising the RGD motif would have any effect on penton

binding to α_v integrin. The specification is further silent in regards to the structure or characteristics of any antibody that binds to penton and is capable of bypassing the interaction between complexed adenoviral particles and α_v integrin other than an antibody that binds to RGD, such as the DAV-1 antibody. It is noted that all of the working examples provided in the specification utilize the DAV-1 antibody. Therefore, based on the nature of penton interaction with α_v integrin, the lack of guidance provided by the specification or the prior art of record as to antibody which do not bind to an RGD motif in penton and which are capable of blocking penton binding to α_v integrin on the cell surface, the limitation of the specification's working examples to antibodies which specifically bind to the RGD motif in penton, and the breadth of the claims, it would have required undue experimentation to practice the scope of the invention as claimed.

Claim Rejections - 35 USC § 103

The rejection of claims 2-16, 18-27, 30, 32-34, 36-37, and 40-45 under 35 U.S.C. 103(a) as being unpatentable over WO 98/40508 (9/17/98), hereafter referred to as Sosnowski et al. in view of Seggern et al. (1999) J. Virol., Vol. 73(2), 1601-1608, Wickham et al. (1996) J. Virol., Vol. 70(10), 6831-6836, and Stewart et al. (1997) EMBO J., Vol. 16, No. 6, 1189-1198, is withdrawn in view of applicant's arguments and amendments to the claims limiting the antibody to an antibody which binds to penton, such that interaction between penton and integrin is bypassed.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. The examiner can be reached Monday- Friday from 10:30-7:00 EST. If the examiner is not available, the examiner's supervisor, Amy Nelson, can be reached at (571) 272-0804. For all official communications, the technology center fax number is (703) 872-9306. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER